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Efficacy and Safety of Spironolactone in Acute Heart Failure: The ATHENA-HF Randomized Clinical Trial

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Abstract

Importance—Persistent congestion is associated with worse outcomes in acute heart failure (AHF). Mineralocorticoid receptor antagonists at high doses may relieve congestion, overcome diuretic resistance, and mitigate the effects of adverse neurohormonal activation in AHF.

Objective—To assess the impact of high dose spironolactone in addition to usual care on N-terminal pro-B-type natriuretic peptide (NTproBNP) levels compared to usual care alone.

Design—Double blind, placebo (or low dose)-controlled, multicenter, randomized clinical trial

Setting—Twenty-two acute care hospitals in the Unites States

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Trial Registration: Clinicaltrials.gov identifier: NCT02235077

The principal investigator Dr. Butler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Participants—Patients with AHF and NTproBNP level of ≥1000 pg/mL or B-type natriuretic peptide ≥250 pg/mL regardless of ejection fraction, previously receiving no or low-dose (12.5 or 25 mg daily) spironolactone

Intervention—High dose spironolactone (100 mg) vs. placebo or 25 mg spironolactone (usual care) daily for 96 hours

Main Outcomes Measures—The primary endpoint was change in NTproBNP levels from baseline to 96 hours. Secondary endpoints included clinical congestion score, dyspnea assessment, net urine output, and net weight change. Safety endpoints included hyperkalemia and changes in renal function.

Results—A total of 360 patients were randomized (median age 65 years, 36% women, 65% Caucasian, and median left ventricular ejection fraction of 34%. Baseline median NTproBNP levels were 4601 (2697, 9596) pg/ml in the high-dose spironolactone group and 3753 (1968, 7633) pg/ml in the usual care group. There was no significant difference in the log NTproBNP reduction between the two groups (−0.55 [−0.92, −0.18] with high-dose spironolactone and −0.49 [−0.98, −0.14] with usual care, P=0.57). None of the secondary endpoint or day-30 all-cause mortality or heart failure hospitalization rate differed between the two groups. The changes in serum potassium and estimated glomerular filtration rate at 24, 48, 72, and 96 hr. were similar between the two groups.

Conclusion and Relevance—Addition of high dose spironolactone to usual care in patients with AHF for 96 hours was well tolerated but did not improve either the primary or any of the secondary efficacy endpoints.

Keywords

Acute heart failure; aldosterone; heart failure; hospitalization; mineralocorticoid receptor antagonist; natriuretic peptide; spironolactone

Acute heart failure (AHF) accounts for over a million hospitalizations in the United States annually.[1] Hospitalizations for HF are associated with a mortality or readmission risk of ~30% at 60-days and ~50% by 6-month post discharge.[2, 3] The already activated renin-angiotensin-aldosterone-system (RAAS) in chronic heart failure may be further accentuated in AHF.[4] The use of intravenous loop diuretics intensifies secondary hyperaldosteronism in these patients.[5] Beyond myocardial and vascular adverse effects, hyperaldosteronism directly contributes to diuretic resistance in AHF.[6] Elevated aldosterone levels in AHF are associated with increased risk of cardiovascular mortality and HF readmission.[7]

The role of low dose mineralocorticoid receptors antagonists (MRA) therapy as a neurohormonal antagonist is well established for the treatment of chronic heart failure and reduced ejection fraction. However, the role of high dose MRA therapy in AHF remains uncertain. Several studies have shown that mineralocorticoid receptors antagonists (MRA) at high doses result in significant natriuresis and help overcome diuretic resistance.[8, 9] However, there have been concerns regarding hyperkalemia and renal failure with MRA use especially with high doses.[10] A single-center, single-blind, non-randomized, trial suggested benefit with high dose MRA therapy in AHF, including lower natriuretic peptide levels, less

congestion, better renal function, and less need for intravenous diuretic.[11] Accordingly, we performed the Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure (ATHENA-HF) trial to test the hypothesis that high dose spironolactone use in patients with AHF will have a beneficial impact in patients with AHF.

METHODS

Study Oversight

The ATHENA-HF trial was sponsored by the National Heart, Lung, and Blood Institute and conducted by the Heart Failure Clinical Research Network. The protocol was approved by the network's protocol review committee and monitored by the network's data and safety monitoring board. The ethics committee at each participating site approved the trial. Data collection, management, and analysis were performed at the network's coordinating center at Duke Clinical Research Institute. All authors reviewed and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of this report to the study protocol, which is available with the full text of this article.

Study Patients

The eligibility criteria for the ATHENA-HF trial included a clinical diagnosis of heart failure with at least one sign and one symptoms of AHF and with an NT-proBNP level of ≥1000 pg/mL or BNP ≥250 pg/mL, regardless of ejection fraction, measured within 24 hours of randomization. Patients were eligible if they were either (1) receiving no spironolactone or (2) receiving low-dose spironolactone (12.5 or 25 mg per day) at home prior to admission. Patients were also required to have serum potassium concentration ≤5.0mmol/L, estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2 and systolic blood pressure >90 mmHg. Patients receiving eplerenone were excluded since in an acute setting it may not be easily known if the patient had previously been intolerant to spironolactone. Patients already taking more than 25 mg of spironolactone were excluded.

Study Design

Detailed study design for the ATHENA-HF trial has been described previously.[12] Briefly, this was a randomized, double blind, placebo controlled trial assessing the impact of high dose spironolactone in addition to usual care vs. usual care on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at 96 hours among patients hospitalized for AHF. The study intervention was initiated within 24 hours of the first dose of intravenous diuretics. Patients not on spironolactone were randomized to 100 mg spironolactone or placebo. Those on low dose spironolactone prior to admission were randomized to 100 mg or 25 mg per day in the usual care alone arm; placebo was not given to these patients to avoid ethical concerns with discontinuing chronic stable therapy. Randomization was double-blind for both comparator strata and was not stratified according to previous low-dose spironolactone. All other medications, including diuretics, were left at the discretion of the treating physician. The study drug was discontinued after 96 hours and further MRA use was left to the treating physician's discretion. Data on left ventricular ejection fraction measured within 6 months prior to randomization were collected; when unavailable, it was

assessed during hospitalization. Algorithms were suggested for the management of worsening creatinine and hyperkalemia during the blinded period.

Study Endpoints

The primary endpoint was the proportional change in the log NT-proBNP levels from randomization to 96 hours (or at discharge if discharge was earlier than 96 hours). Multiple secondary endpoints from randomization to 96 hours were assessed. These included: a) clinical congestion score, calculated by summing the individual scores for orthopnea, jugular venous distension, and pedal edema on a standardized 4-point scale ranging from 0 to 3;[13] b) dyspnea relief, measured by a Likert scale (ranging from 1=markedly improved to 7= markedly worse) and by the Visual Analog Scale (ranging from 0 to 100, with higher values indicating better status); c) cumulative net urine output on a daily basis for up to 96 h; d) net weight change from baseline to 96 h or discharge (whichever came first); e) furosemide equivalents of loop diuretic dose at discharge, and f) development of in-hospital worsening HF, with signs and symptoms requiring additional therapy. Exploratory endpoints included a day-30 post randomization composite of all-cause mortality, all-cause readmission, or outpatient worsening heart failure (heart failure related readmission or emergency department visit or need for outpatient intravenous diuretics). Participants were also contacted by telephone at 60±3 days to assess vital status. Safety endpoints included change in serum creatinine, estimated glomerular filtration rate, and incidence of moderate (>5.5mmol/L) and severe hyperkalemia (>6.0mmol/L) during the 96-hour treatment period.

Statistical Analysis

It was anticipated that 25% of subjects enrolled would be on low-dose MRA at randomization. Assuming a 20% further reduction in NT-proBNP from randomization in the MRA group compared to placebo and a 10% reduction in those on low-dose MRA at baseline, yielded an overall benefit of 17.5% for the study population. With a 1:1 randomization and a two-sided type I error rate of 0.05, a total of 360 subjects provided approximately 85% power. Randomization was conducted using a permuted block design with stratification based on site and MRA usage at enrollment. The primary analysis used a linear regression model with an indicator variable for treatment assignment, an indicator for MRA use prior to admission, and the log of the baseline NT-proBNP level. We opted to analyze log-transformed NT-proBNP levels because of better distributional properties and therefore improvements in the underlying assumptions of the statistical models involving NT-proBNP. Missing values of the 96-hour NT-proBNP levels (22 in usual care and 23 in high dose spironolactone group) were imputed using a multiple imputation algorithm. In a sensitivity analysis, values missing due to death were imputed to the worst possible value.[14] This analysis accounted for low-dose MRA prior to admission using a stratified version of the Wilcoxon-Mann-Whitney test. For binary outcomes, chi-square tests and Fisher's exact test were used for unadjusted comparisons. Unadjusted time-to-event comparisons were conducted using Kaplan-Meier survival estimates and log-rank tests. Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Four pre-specified subgroup analyses were conducted including baseline low dose MRA use, gender, ejection fraction (greater than versus less than or equal to 45%), and age (greater than versus equal to or less than 65 years). Data are presented as median

(interquartile range [IQR]). For primary and secondary end points, a P value less than .05 was considered significant. For subgroup analyses, a treatment by subgroup interaction p less than .01 was considered significant. All analyses were conducted with the use of SAS statistical software version 9.2.

RESULTS

Study Patients

From December 2014 to April 2016, 360 patients were enrolled from 22 sites for an enrollment rate of ~1 patient/site/month. A total of 182 patients were randomized to high-dose spironolactone plus usual care and 178 to usual care alone (placebo N=132 or continued low dose spironolactone N=46) Figure 1. Baseline characteristics of the patient population are shown in Table 1. Note that the use of medication at baseline reflects those that the patients were given at randomization, which was within 24 hours of first dose of I.V. diuretics. The number of patients on spironolactone was lower at randomization than pre-admission as home medications were discontinued at admission for some patients. The median age was 65 years, 36% were females, and 56% were White. Median ejection fraction was 34%; 93 patients (26%) had ejection fraction >45%. Median systolic blood pressure was 122 mmHg, heart rate was 79 bpm, serum potassium concentration was 4.0 meq/L, serum creatinine was 1.2 mg/dl, and estimated glomerular filtration rate (eGFR) was 56 ml/min.

Efficacy

Baseline median (interquartile range) NTproBNP levels were 4601 pg/ml (IQR, 2697, 9596 pg/ml) in the spironolactone and 3753 pg/ml (IQR, 1968–7633 pg/ml) in the usual care group. All randomized patients completed the study. There was no significant difference in the primary endpoint between the two groups (log NTproBNP change −0.55; −0.92, −0.18 in the spironolactone and −0.49; −0.98, −0.14 in the usual care arm; P=0.57). Changes in log NT-proBNP were similar in analyses using only complete cases, i.e. without imputation (−0.56; −0.96, −0.19 in the spironolactone and −0.50; −0.99, −0.14 in the usual care arm; P=0.57). None of the secondary endpoint including dyspnea score (Likert and Visual Analog scales), clinical congestion score, net urine output, weight change, requirement for loop diuretics, and in hospital worsening heart failure were different between the two groups (Table 2). Of note, NT-proBNP levels in Table 1 (on-site qualification values before randomization) vs. Table 2 (core lab values before treatment initiation) were drawn at different times and patients in the two groups may have had different treatments and responses to them in the interim. At discharge, mean furosemide dose (in IV furosemide equivalents) was 89.5 mg in the spironolactone vs. 98.0 mg in the placebo group. In the spironolactone group, 26 patients (14%) were discharged on spironolactone (1 on 50 mg, 17 on 25 mg, and 8 on 12.5 mg) vs. 35 (20%) in the placebo group (2 on 50 mg, 25 on 25 mg, and 8 on 12.5 mg). At 96 h, thiazide use was 3% in the usual care and 4% in the high-dose spironolactone group. Median time from randomization to discharge was 4 (2, 7) days in both groups. Two and 7 patients in the usual care and, 2 and 5 in high-dose spironolactone group died during the index hospitalization and through day 30 respectively. There was no difference in time to first heart failure readmission, emergency visit, or death between the two groups (adjusted HR 1.22, 95%CI 0.68, 2.19; P=0.50; Figure 2). There was no

difference in all-cause mortality at day-60. There was no difference in day-30 MRA use between the two groups (36% usual care alone vs. 31% high-dose spironolactone group, p=0.24).

Safety

High dose spironolactone was well tolerated. The changes in serum potassium, creatinine, and estimated glomerular filtration rate from baseline to 24, 48, 72, and 96 hr is shown in Table 3. Only one patient in the usual care group and none in the high dose spironolactone group experienced serum potassium levels between 5.5–5.9 mmol/L and no one had potassium concentration > 6.0 mmol/L during the 96 hours of study treatment. Serious adverse events by day-30 were reported in 84 (47%) patients in the usual care group and 79 (43%) patients in the high-dose spironolactone group (P=0.47). Worsening renal function, defined as an increase of 0.3 mg/dl in creatinine from baseline through 96 hours, occurred in 51/182 (28%) in the high-dose spironolactone group and 57/178 (32%) in the usual care group (P=0.42). No differences between groups were observed in terms of changes in heart rate or blood pressure levels during treatment.

Sub-Group Analysis

No differences were observed in the primary endpoint between patients randomized to high dose spironolactone or usual care stratified by age, gender, or use of low dose spironolactone at baseline (Supplementary Figure). The change in log NTproBNP levels at 96 hours or at earlier discharge in the spironolactone and usual care groups respectively among patients with ejection fraction ≤45%was −0.55 (−0.92, −0.19) and −0.54 (−0.99, −0.15), and in those with ejection fraction >45% was −0.53 (−1.03, −0.14) and −0.42 (−0.64, −0.03) (interaction P=0.078). The results were similar when only complete cases were analyzed without imputation (ejection fraction ≤45%: spironolactone −0.56 [−0.92, −0.20] vs. usual care −0.56 (−1.01, −0.15]; ejection fraction >45%: spironolactone −0.57 [−1.11, −0.19] vs. usual care −0.43 [−0.64, −0.09]).

DISCUSSION

In this study, which represents the first double blind multicenter trial assessing the efficacy and safety of high dose spironolactone in AHF, there was no benefit or risk seen with active intervention over usual care on either the primary or any of the secondary endpoints. These include changes in NTproBNP levels, urine output, weight changes, symptoms or congestion score. These results are in contrast to some of the earlier mechanistic and clinical data that suggested increased urine output and less congestion with the use of high dose MRA therapy. High dose spironolactone therapy was well tolerated without any significant risk of hyperkalemia or worsening renal function in the population of patients who met the eligibility criteria for the ATHENA-HF trial.

The eligibility criteria for ATHENA-HF were chosen to represent a generalizable AHF population. The inclusion criteria of glomerular filtration rate >30 ml/min resulted in a cohort with a median rate of 56 ml/min. Both study groups had significant diuresis and lost over 6 lbs. of weight in the first 96 hr. or by earlier discharge. It is possible that targeting

diuretic resistant patients with lower glomerular filtration rate may lead to better results with high dose spironolactone. No difference was seen in the use of diuretic doses between the two study arms, so it does not appear that high-dose spironolactone led to a selective early reduction in loop diuretic doses in the active intervention. No differences were noted between patients who were MRA naïve vs. those on low dose spironolactone at baseline and hence the neutral results cannot be attributed to chronic MRA use in a proportion of patients. Is it possibility that 100 mg spironolactone is not a high enough dose and that higher doses are needed. This possibility is intriguing considering that previous smaller heart failure studies have used up to 200 mg of spironolactone similar to the doses used in cirrhosis.[8] This approach may be explored in the future considering the safety of 100 mg spironolactone in the ATHENA-HF trial. Emerging data with novel potassium binders reducing the risk of hyperkalemia may further facilitate such a study.[10] Spironolactone is a prodrug that is converted to active metabolite canrenone, which is responsible for its mineralocorticoid effects.[15] Considering the short duration of AHF hospitalizations in the United States averaging at 4–5 days,[16] using intravenous canrenoate with faster onset of action may be more beneficial. Similarly, new non-steroidal MRA finerenone that does not require conversion to an active metabolite may be more useful in the AHF setting.[17]

There were no safety concerns raised by the use of high dose spironolactone in this trial. There is a substantial risk of hyperkalemia even with lower doses of spironolactone in patients with chronic heart failure.[10] With the active changes in glomerular filtration rate and blood pressure commonly encountered in the setting of AHF, the risk of hyperkalemia with high dose spironolactone is of concern. However, our study confirms that in the hospital setting high dose spironolactone use is safe in patients with relatively preserved renal function and with the implementation of other precautions and protocols such as those used in this trial. These data are encouraging for future research with either higher dose MRA in AHF than used in ATHENA HF, or in patients with worse renal function and diuretic resistance.

There were no differences in the efficacy or safety of high dose spironolactone therapy in any of the pre-specified sub-groups based on age, gender, or previous use of MRA. Interesting, while no differences were seen among patients with ejection fraction ≤45%, in patients with ejection fraction >45%, spironolactone intervention led to a numerically higher reduction in log NTproBNP levels with a trend toward a significant treatment-by-subgroup interaction. Though the trial was not powered to assess differences among patients with reduced vs. preserved ejection fraction, these data are intriguing as the Renal Optimization Strategies Evaluation (ROSE) trial also showed a differential trend with low dose dopamine use in AHF patients between those with preserved vs. reduced ejection fraction.[18] While it is a standard for chronic heart failure trials to study patients with reduced and preserved ejection fraction separately, a number of recent AHF trials have included patients regardless of ejection fraction. The results of the ATHENA-HF trials provide data to encourage further study of the differences between these two patient populations in the AHF setting.

Our study has several limitations. First, the duration of the treatment (96 h or until discharge, whichever came first) was relatively short. Considering that spironolactone may take few days to convert to its active metabolites, especially in the presence of hepatic congestion, we

cannot exclude the possibility that longer treatment duration may have shown differences between the two groups. Second, data on the primary endpoint (change in NT-proBNP levels) were missing for approximately 12% of the study population. However, imputed, worst-possible-value, and raw analyses all pointed to a neutral effect of spironolactone on NT-proBNP levels. Third, in order for the trial to represent better the real-world population with AHF, we included a number of patients (25%) already receiving low-dose MRA at home and this may have influenced the treatment effect, thus contributing towards the neutral results. Of note, there was no differential effect of high-dose spironolactone between low-dose and no baseline MRA strata. Fourth, our study was not powered to explore differences according to ejection fraction. Finally, we excluded patients with glomerular filtration rate ≤30 ml/min and therefore our results, especially regarding safety, cannot be extrapolated to these patients.

In conclusion, high dose spironolactone in AHF was not associated with improvement in either the primary or the secondary outcomes in the ATHENA-HF trial. This intervention was safe and well tolerated. Future research should study higher doses and patients with diuretic resistance and should explore differences between patients with preserved vs. reduced ejection fraction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

Question

Does addition of high-dose spironolactone in patients with acute heart failure lower natriuretic peptide levels and improve outcomes better than usual care?

Findings

High-dose spironolactone use in acute heart failure was not associated with improvement in natriuretic peptide levels, symptoms, congestion, urine output, weight loss, or clinical outcomes than usual care group.

Meaning

Routine use of high-dose spironolactone in acute heart failure is not recommended. Further studies targeting specifically diuretic resistant patients with high-dose spironolactone are needed.

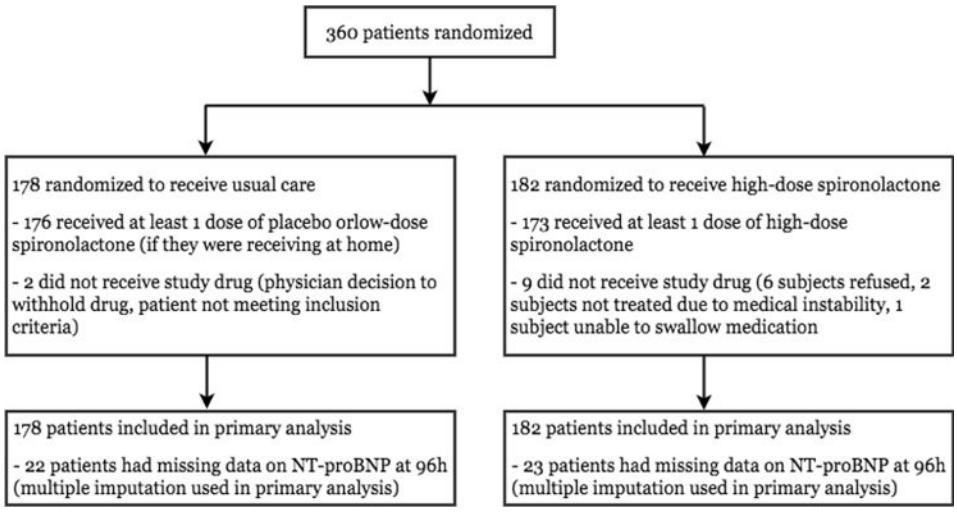

Figure 1.
CONSORT Flow Diagram

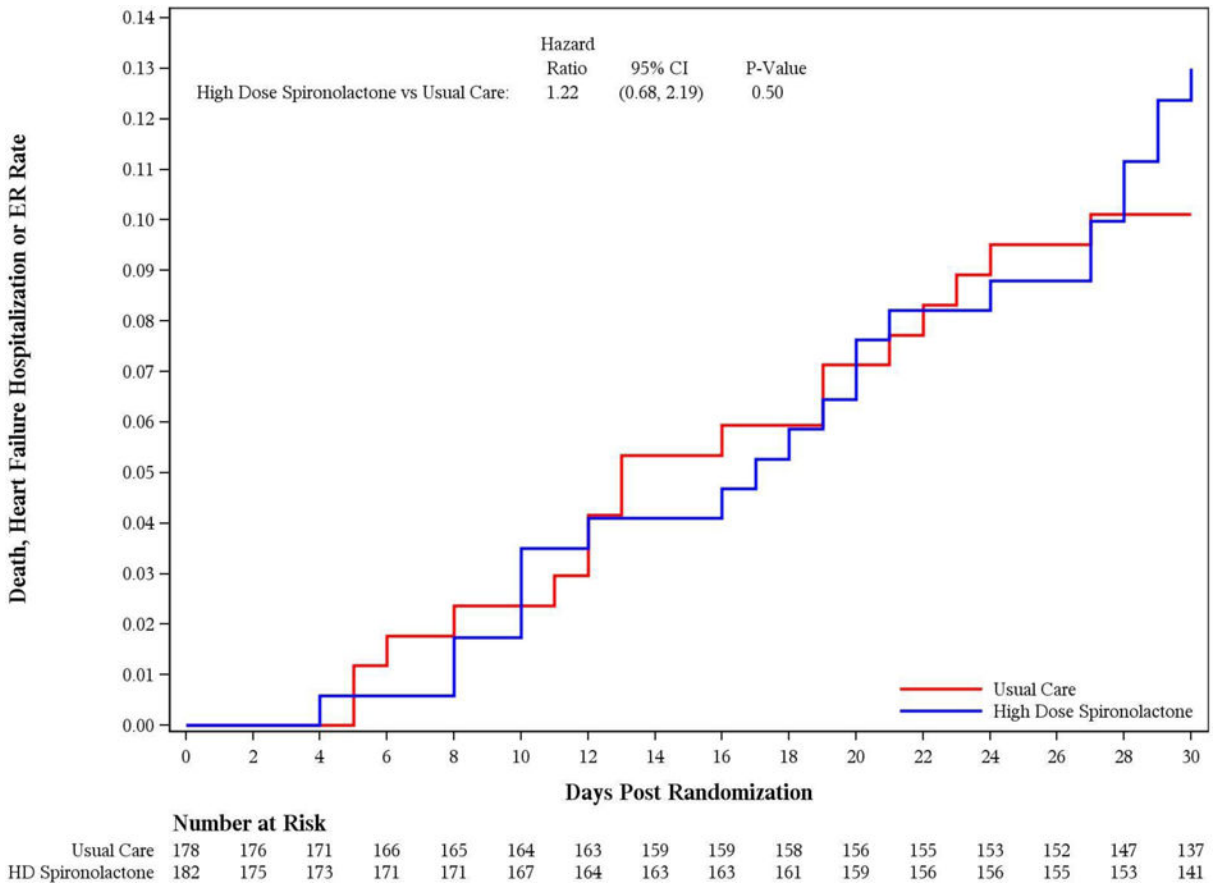

Figure 2. Time to first heart failure re-hospitalization, emergency room visit, or death

There were no significant differences noted in the post-discharge outcomes among patients randomized to the usual care alone vs. the high-dose spironolactone group

Table 1

Baseline Patient Characteristics

Baseline Characteristics	Usual care alone (N=178)	High-dose spironolactone (N=182)
Demographics		
Age (yr.)	65 (54, 74)	65 (57, 76)
Female - no. (%)	64 (36)	65 (36)
Race		
White - no. (%)	99 (56)	101 (55)
Black - no. (%)	77 (43)	74 (41)
Others - no. (%)	2 (1)	7 (4)
Hispanic or Latino - no. (%)	6 (3)	2 (1)
Past Medical History – N (%)		
Myocardial Infarction	52 (30)	51 (28)
Hypertension	142 (81)	159 (87)
Stroke	26 (15)	29 (16)
Atrial fibrillation	84 (48)	88 (50)
Chronic Lung Disease	43 (24)	39 (21)
Diabetes Mellitus	74 (42)	72 (40)
Chronic Kidney Disease	54 (31)	43 (24)
Obstructive Sleep Apnea	41 (25)	41 (25)
Current smoker	25 (15)	31 (17)
Baseline Treatment - N (%)[a]		
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker	112 (63)	105 (58)
Beta blockers	132 (74)	135 (74)
Mineralocorticoid receptor antagonists	21 (12)	19 (11)
Loop diuretics	169 (95)	177 (97)
Furosemide equivalent dose (median, mg)	80 (40, 160)	80 (40, 160)
Furosemide equivalent dose (mean, mg)	118.8 ± 94.4	122.5 ± 113.8
Thiazide diuretics	3 (2)	3 (2)
Digoxin	19 (11)	15 (8)
Hydralazine	47 (26)	44 (24)
Long-acting Nitrates	33 (19)	35 (19)
Calcium channel blockers	23 (13)	36 (20)
Statin	101 (57)	104 (57)
Implanted defibrillator	35 (42)	23 (35)
Biventricular pacemaker	31 (37)	28 (42)
Clinical Characteristics		
Heart failure hospitalizations in past year, no. (%)	114 (64)	120 (66)
Left ventricular ejection fraction – no. (%)	30 (20, 45)	35 (21, 50)

Baseline Characteristics	Usual care alone (N=178)	High-dose spironolactone (N=182)
Proportion with ejection fraction <45% – no (%)	140 (79)	123 (69)
Ischemic etiology - no. (%)	117 (66)	109 (60)
Systolic blood pressure - mmHg	123 (108, 138)	120 (106, 138)
Heart rate per minute	80 (70, 94)	78 (70, 90)
Body mass index kg/m^2[b]	32 (27, 38)	30 (25, 35)
Jugular venous pulse ≥10 cm - no. (%)	126 (74)	135 (76)
Rales - no. (%)	99 (56)	112 (62)
Edema - no. (%)	142 (80)	139 (77)
Orth0pnea - no. (%)	154 (87)	151 (85)
New York Heart Association Class III or IV - no. (%)	153 (86)	149 (85)
Fatigue frequent or continuous – no (%)	151 (86)	156 (86)
Dyspnea frequent or continuous – no (%)	151 (86)	150 (83)
Dyspnea – visual analog scale	65 (40, 75)	60 (45, 75)
Laboratory Values		
Sodium - mEq/L	140 (138, 142)	140 (138, 142)
Potassium - mEq/L	4.0 (3.6, 4.3)	3.9 (3.6, 4.3)
Blood urea nitrogen - mg/dL	22 (17, 31)	23 (16, 33)
Creatinine - mg/dL	1.3 (1.0, 1.5)	1.2 (1.0, 1.5)
Glomerular filtration rate - ml/min/1.73 m^2	55 (46, 71)	58 (45, 75)
B-type natriuretic peptide, pg/ml (N=156)[c]	1055 (502, 1581)	1131 (680, 1986)
N-terminal pro B-type natriuretic peptide, pg/ml (N=204)[c]	4176 (1936, 7456)	(2472, 10048)

Values shown are median (25th, 75th) or count (%)

[a] At the time of randomization

[b] p<0.05

[c] Site-based qualifying values

Table 2

Primary and Secondary Outcomes

Outcomes	Usual care Alone	High dose spironolactone	P
Primary endpoint Log N-terminal pro B-type natriuretic peptide			
Baseline	8.23 (7.58, 8.94)	8.43 (7.90, 9.17)	
96 hours (or earlier discharge) – with multiple imputation for missing values	7.64 (6.93, 8.45)	7.89 (7.19, 8.68)	
Change - with multiple imputation for missing values	−0.49 (−0.98, −0.14)	−0.55 (−0.92, −0.18)	0.57
96 hours (or earlier discharge) – no imputation, complete cases only	7.55 (6.91, 8.31)	7.81 (7.06, 8.59)	
Change - with multiple imputation for missing values	−0.50 (−0.99, −0.14)	−0.56 (−0.96, −0.19)	0.57
Secondary endpoints N-terminal pro B-type natriuretic peptide, pg/ml			
Baseline	3753 (1968, 7633)	4601 (2697, 9596)	
96 hours (or earlier discharge) – with multiple imputation for missing values	2080 (1025, 4675)	2672 (1326, 5896)	
Change - with multiple imputation for missing values	−1072 (−3182, −231)	−1796 (−3883, −571)	0.76
96 hours (or earlier discharge) – no imputation, complete cases only	1898 (1003, 4046)	2461 (1168, 5366)	
Change - with multiple imputation for missing values	−1060 (−2856, −238)	−1774 (−3763, −586)	0.61
Clinical congestion score			
Baseline	11 (9, 12)	10 (9, 12)	
96 hours (or earlier discharge)	4 (2, 6)	4 (2, 7)	
Change	−6 (−8, −4)	−6 (−8, −4)	0.41
Dyspnea			
Likert Score (96 hours or earlier discharge)	2 (1, 3)	2 (1, 3)	0.31
Visual Analog Scale			
Baseline	65 (40, 75)	60 (45, 75)	
96 hours (or earlier discharge)	83 (70, 90)	80 (65, 90)	
Change	15 (5, 30)	15 (2, 30)	0.61
Net urine output, ml (cumulative)			
24 h	1183 (510, 1955)	1100 (483, 2131)	0.76
48 h	2282 (1155, 4135)	2484 (1203, 4411)	0.44
72 h	3810 (2011, 5565)	4171 (2053, 6040)	0.53
96 h	5584 (2924, 8132)	6086 (2780, 8420)	0.57
Weight change, Ibs			
Baseline	207.1 (171.0, 250.4)	195.0 (162.6, 237.0)	
96 hours (or earlier discharge)	198.9 (167.6, 243.6)	185.1 (158.5, 230.8)	
Change	−6.1 (−11.2, −1.8)	−7.3 (−13.0, −2.0)	0.33
Furosemide equivalent diuretic dose, mg			
Baseline	160 (120, 320)	160 (100, 320)	
96 hours (or earlier discharge)	80 (40, 240)	80.0 (40, 200)	
Change	−80 (−160, 0.0)	−80.0 (−160, 0)	0.77
Worsening heart failure, N (%)			

Outcomes	Usual care Alone	High dose spironolactone	P
Inpatient	31 (18)	33 (19)	0.76
Outpatient (through day 30)	17 (10)	19 (11)	0.76

Values shown are median (25^{th}, 75^{th}) or count (%).

Table 3

Changes in serum potassium concentration and renal function

	Usual care alone	High dose spironolactone	Usual care alone	High dose spironolactone	P
	Median			Mean	
Change in serum potassium – mEq/L					
24 h	0.00 (−0.40, 0.30)	0.00 (−0.30, 0.30)	0.01 ± 0.56	−0.00 ± 0.47	0.50
48 h	0.10 (−0.30, 0.40)	0.10 (−0.10, 0.40)	0.04 ± 0.52	0.16 ± 0.46	0.02
72 h	0.20 (−0.40, 0.55)	0.20 (−0.20, 0.60)	0.09 ± 0.62	0.22 ± 0.52	0.08
96 h	0.20 (−0.30, 0.60)	0.30 (0.00, 0.70)	0.15 ± 0.69	0.31 ± 0.54	0.08
Change in serum creatinine - mg/dL					
24 h	0.05 (−0.05, 0.20)	0.05 (−0.03, 0.17)	0.07 ± 0.18	0.06 ± 0.17	0.76
48 h	0.02 (−1.10, 0.20)	0.10 (−0.03, 0.02)	0.10 ± 0.27	0.09 ± 0.20	0.67
72 h	0.08 (−0.08, 0.22)	0.10 (−0.03, 0.28)	0.13 ± 0.33	0.12 ± 0.26	0.85
96 h	0.10 (−0.02, 0.33)	0.10 (−0.05, 0.27)	0.16 ± 0.30	0.15 ± 0.30	0.77
Change in estimated glomerular filtration rate - ml/min/1.73 m^2					
24 h	−1.95 (−8.46, 2.79)	−2.58 (−7.83, 1.53)	−2.75 ± 9.43	−2.54 ± 10.80	0.87
48 h	−1.59 (−9.65, 3.71)	−4.12 (−8.87, 1.89)	−3.34 ± 12.52	−3.33 ± 11.15	0.95
72 h	−3.70 (−12.06, 4.09)	−3.71 (−10.67, 0.87)	−4.47 ± 13.37	−4.53 ± 12.05	0.82
96 h	−5.53 (−13.11, 0.79)	−4.35 (−11.06, 1.74)	−5.56 ± 13.85	−4.13 ± 11.58	0.56